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Isolation of effect of the Individual Compounds in a Combination Regimen

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Why are we discussing this topic?

- To isolate the individual contribution in a combination A+B is necessary to establish the benefit/risk profile for that combination
  - It needs to be ruled out that one of the individual components alone is responsible for the efficacy
  - Ideally a pivotal registration study would be A+B vs A vs B, but what if the SOC is C?
  - Can the ph3 registration study be A+B vs C instead of doing a 3- or 4-arm study?
    - In general?
    - In certain situations?
- What do the guidelines say? Do they provide the answer?

US

- **US Guidance** for Industry "Codevelopment of two or more new investigational drugs for use in combination" (June 2013) outlines
  - Need for clear biological rationale for why a combination is preferable over using the individual components
  - Compelling reason for not developing the components individually
  - Non-clinical characterization of the activity of each compound and or non-clinical models providing evidence that the combination will have superior efficacy over the individual components
  - Clinical studies need to confirm that each component contributes to the activity of the combination
  - Studies with multiple arms, eg in ph2 can help to avoid providing that evidence in ph3
    - It could be possible to drop individual arms, eg when it becomes clear they have insufficient activity on their own
- If contribution of each individual compound has been "**adequately demonstrated** in vivo, in vitro and/or in ph2 studies" … "… then ph3 studies comparing the combination vs placebo or SOC … could be sufficient to establish effectiveness"

EU

- "Guideline on the evaluation of anticancer medicinal products in man", **CHMP** (rev 5, Sep 2017) outlines
  - If the experimental agent (A) is added to an established regimen (B), superiority of AB vs. B should be demonstrated, traditionally, not include A alone arm…
  - **Uncommonly**, an entirely new combination AB is tested against a reference regimen. In these cases, **solid non-clinical and clinical phase I/II data** should support **the need for both components** in the experimental regimen.

Examples of "A+B vs C (SoC)"

- Pembrolizumab + axitinib vs sunitinib in 1st line RCC
  - Clear clinical improvements on several effcacy endpoints for A+B vs C
  - Sufficient 'supportive evidence' from 2 ph2 studies: pembro+axitinib vs axitinib shows better ORR and PFS and pembro monotherapy also shows a reasonable ORR supporting activity
  - But each individual component shows clearly lower activity than the combination (though across studies)
- Avelumab + axitinib vs sunitinib in 1st line RCC
  - Clear clinical improvements on several effcacy endpoints for A+B vs C (PFS; ORR; OS positive trend)
  - Supporting ph2 studies show response rates (and PFS) supportive of individual activity but clearly lower than what the pivotal study has shown for the combination
  - "…available data are considered sufficient to justify the contribution of each agent to the overall activity of the proposed regimen…"

Examples of "Multiple Combinations, A+B+C vs SoC"

- Ipilimumab + Nivolumab in 1st line RCC showing OS improvement vs sunitinib
  - Considered clinically meaningful
  - Combination already approved in melanoma
  - Sound non-clinical evidence demonstrating synergy with Ipi and Nivo and Ph1/2 monotherapy data in RCC provided
  - Need for evidence that both Ipi and Nivo are needed (again) in RCC?

- Encorafenib + binimetinib
  - In melanoma clear clinical improvement of enco 450 +bini vs enco 300 vs vemurafenib
  - Sufficient 'supportive evidence' from ph2: enco 300 + bini vs enco 300 (PFS and ORR advantage at interim)
  - Recently Beacon study reported where Encorafenib + binimetinib + cetuximab show significant OS and ORR improvement over SOC (Folfiri +cetuximab) in 2nd/3rd line CRC

Despite Guidelines …

… Questions remain:

Is fully powered evidence in each tumour type really needed when individual contribution has been demonstrated

- in earlier phase studies or
- adequately in non-clinical setting or
- in other tumour types or
- other lines other disease?

- What about the situation where A (and/or B) are approved as monotherapy or in combination eg in a later line of treatment when the target indication is 1st line or adjuvant treatment?
- What about the situation where A (and/or B) are approved as monotherapy or in combination in a different indication?
- How to address this topic if there is immediately a ph3 study following ph1 after early study suggests very significant clinical activity?

A Potential Way Forward
(Discussed at March 2019 FoCR)

A – novel IO

B – novel PD-1

C – approved PD-1

A+B – novel combination

1:1:1:1 randomisation

Interim Analysis

ORR – pre-specified criteria

Drop arm C

A – novel IO therapy

B – novel PD-1

A+B – novel combination

Final Analysis

OS Endpoint

A+B vs B

A vs B

In Summary

- Isolation of effect of individual components in a combination therapy continues to be a relevant topic in (oncology) drug development today, in particular in the context of new classes of therapies intended to demonstrate transformational benefit
- Regulatory Guidelines provide general help
- In the ph3 setting it may be unethical to expose patients to potentially suboptimal therapy(ies) (eg monotherapy Arm A or B)
- Practical examples and evidence from Regulatory reviews show the challenges

Can the CDDF multi-stakeholder discussion provide creative guidance for the future?!